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Award Number: W8XWH-05-1-0236

TITLE: A Novel Approach for the Identification of Pharmacophores through Differential Toxicity Analysis of Estrogen Receptor Positive and Negative Cell Lines

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REPORT DATE: July 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-07-2007	Annual	1 Jul 2006 – 30 Jun 2007

4. TITLE AND SUBTITLE

A Novel Approach for the Identification of Pharmacophores through Differential Toxicity Analysis of Estrogen Receptor Positive and Negative Cell Lines

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-05-1-0236

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Louisville Research Foundation
Louisville, KY 40014

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This grant was award to the PI at Louisiana State University. He left there in Aug 2006 and with the assistance of Grant Manager, Dr. Carole Christian, it was transferred to the University of Louisville where he started Apr 2007. Minimal work was done on the project prior to departure from LSU and minimal funds were expended. This project was essential to my obtaining an appointment as an Associate Professor of Medicine at the University of Louisville's James Graham Brown Cancer Center, along with significant startup package, and my involvement as a Project PI on the Brown Cancer Center's NIH-funded Molecular Targets Program. Currently, my new laboratory has been equipped with the needed computer hardware and software. I anticipate the postdoctoral fellow hired to participate on the project will start by Aug 6, 2007, and given the revised timeline for this project, I expect that it will be completed on time and as planned.

15. SUBJECT TERMS
Structure-activity relationship modeling, proteomics, drug discovery

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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Introduction

The objective of this project is to employ an innovative approach to discover new molecular targets found only in estrogen receptor positive (ER+) breast cancer cells that are 1) highly associated with cell type-specific toxicity, 2) compounds that influence or interact with them, and 3) ultimately anticancer pharmacophores that uniquely target breast tumor cells to be used as the basis for the design of new anticancer drugs. We observed that certain chemicals display potent toxicity to one type of breast cancer cell line and not other related lines. Based on this observation, the **hypothesis** for the project is that this cell type-specific toxicity is due to an interaction of a chemical agent with a specific molecular target found only in the sensitive cells. The project is defined by two working hypotheses. The **first working hypothesis** is that congeneric sets of compounds that display this excessive and specific toxicity to ER+ cells will influence particular molecular targets found only with the sensitive cell line. The reasoning for this is based on the accepted premise of SAR modeling that like structure begets like activity. The **second working hypothesis** is that, when the proteome of the ER+ cell line is probed with a defined congeneric series of compounds that display this cell type-specific activity, these compounds will all affect, minimally, the same identifiable molecular target. Through the techniques of comparative proteomics, we anticipate being able to identify these unique target(s) and thus provide the basis for highly effective antibreast cancer therapies.

Body

This grant was awarded to the PI at Louisiana State University. He left there in Aug 2006 and with the assistance of Grant Manager, Dr. Carole Christian, the grant was transferred to the University of Louisville where he started Apr 2007. Minimal work was done on the project prior to departure from LSU and minimal funds were expended.

This project was essential to my obtaining an appointment as an Associate Professor of Medicine at the University of Louisville's James Graham Brown Cancer Center, along with significant startup package, and my involvement as a Project PI on the Brown Cancer Center's NIH-funded Molecular Targets Program.

Currently, my new laboratory has been equipped with the needed computer hardware and software described in the proposal. I anticipate the postdoctoral fellow hired to participate on the project will start by Aug 6, 2007, and given the revised timeline for this project, I expect that it will be completed on time and as planned.

Key Research Accomplishments

Not available at this time.

Reportable Outcomes

The PI was able to successfully use the results from his prior Idea award and the applicability of this Idea award to obtain appointments as an Associate Professor of Medicine and Associate Professor of Pharmacology and Toxicology at the University of Louisville's School of Medicine as well as an appointment to its James Graham Brown Cancer Center. Regarding the Brown Cancer Center, in September 2003 it was awarded a five-year, $11 million Center of Biomedical Research Excellence (COBRE) grant from the National Center for Research Resources at the National Institutes of Health under the directorship of Dr. Donald Miller. The grant established the Molecular Targets Program, which the PI is part of by providing for the recruitment of researchers from a variety of disciplines to identify and develop new molecular targets for anti-cancer drugs and therapies using the techniques of modern structural biology.

My appointment at the University of Louisville is tentatively set to start April 1, 2007 and will include a three year COBRE-funded project in Molecular Targets.

Conclusion

My recruitment to the University of Louisville's Brown Cancer Center and my new NIH-supported COBRE project in Molecular Targets places the PI in a good environment to pursue this project and provides him with all the needed resources for its successful completion. The PI's laboratory has been equipped with the needed computer hardware and software and will have a postdoctoral fellow hired to participate on the project by Aug 6, 2007. Given the revised timeline for this project, the PI anticipates it will now be completed on time and as planned.

References

None

Appendices

None